

## INTERNATIONAL COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C. 20231  
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 17 December 1999 (17.12.99)	
<b>International application No.</b> PCT/FI99/00329	<b>Applicant's or agent's file reference</b> LEVO-ORAL1
<b>International filing date</b> (day/month/year) 23 April 1999 (23.04.99)	<b>Priority date</b> (day/month/year) 23 April 1998 (23.04.98)
<b>Applicant</b> LARMA, Ilkka et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
 19 November 1999 (19.11.99)

☐ in a notice effecting later election filed with the International Bureau on:  
 \_\_\_\_\_

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Jean-Marie McAdams  Telephone No.: (41-22) 338.83.38
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>LEVO-ORAL1</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/FI99/00329</b>	International filing date (day/month/year) <b>23/04/1999</b>	Priority date (day/month/year) <b>23/04/1998</b>
International Patent Classification (IPC) or national classification and IPC <b>A61K31/50</b>		
Applicant <b>ORION CORPORATION et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand <b>19/11/1999</b>	Date of completion of this report <b>28.02.2000</b>
Name and mailing address of the international preliminary examining authority:  <b>European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</b>	Authorized officer <b>Heller, D</b>  Telephon No. +49 89 2399 8746 

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/FI99/00329

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-16 as originally filed

**Claims, No.:**

1-10 as originally filed

**Drawings, sheets:**

1/3-3/3 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 1-10.

because:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/FI99/00329

- ☒ the said international application, or the said claims Nos. 1-10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	see sections III and V
	No:	Claims	

**2. Citations and explanations**

**see separate sheet**

**VI. Certain documents cited**

**1. Certain published documents (Rule 70.10)**

and / or

**2. Non-written disclosures (Rule 70.9)**

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application N . PCT/FI99/00329

**SECTION III:**

Claims 1 to 10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**SECTION V:**

**Prior art**

Reference is made to the following documents:

D1 (EP-A-0 383 449) relates to heterocyclic compounds - including levosimendan (p. 3, formula I) and salts thereof as well as new intermediates to compositions containing these compounds and to a process for the preparation of the same. The compounds are useful as cardiotonic agents, antihypertensive agents and vasodilators for the treatment of congestive heart failure (p. 3, ll. 1 to 5). In a conventional way it is possible to make formulations which liberate the active ingredient slowly during a prolonged period of time (p. 6, ll. 42 and 43).

D2 (WO 92 12135 A; cited in the application) relates to salts of the (-) enantiomer of levosimendan, to compositions and to the process for the preparation as well as to new intermediates of this process. The compound according to the invention is useful as cardiotonic agent, antihypertensive and vasodilator for the treatment of congestive heart failure (p. 1, ll. 3 to 10).

D3 (WO 93 21921 A; cited in the application) describes levosimendan and its optically active enantiomers having significant anti-ischemic properties (p. 1, ll. 11 and 12).

**Novelty**

In view of the prior art as summarized above the subject-matter of claims 1 to 10 is novel und Article 33 (2) PCT.

### **Inventive step**

The subject-matter of claims 1 to 10 involves an inventive step in the sense of Article 33 (3) PCT.

D1 which seems to be the closest prior art differs from the present application in that it is silent to the claimed controlled release composition. D1 only mentions that in a conventional way it is possible to make formulations which liberate the active ingredient slowly during a prolonged period of time (p. 6, ll. 42 and 43).

The problem to be solved can be described as how to provide further peroral compositions providing a therapeutical effect over an extended period of time in a controlled release formulation.

The problem was solved by the present application claiming an controlled release composition. Said composition provides an improved oral delivery system for levosimendan compared to conventional immediate release and long-acting preparations including the following advantages:

- reduction of undesired effects of high levosimendan levels such as increased heart rate by lower peak plasma levels
- reduced frequency of administration
- reduced accumulation of active metabolite (II) causing undesired effects

Therefore, present claims 1 to 10 seem to be inventive (Article 33 (3) PCT).

### **Industrial applicability**

For the assessment of the present claims 1 to 10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/FI99/00329

**SECTION VI:**

D4 (WO99/16443) does not constitute prior art within the meaning of Rule 64.1 (b) PCT. It does not appear to be relevant to the claims of the present application.

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>LEVO-ORAL1</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/FI 99/ 00329</b>	International filing date (day/month/year) <b>23/04/1999</b>	(Earliest) Priority Date (day/month/year) <b>23/04/1998</b>
Applicant <b>ORION CORPORATION et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.  
☒ It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.

☒ None of the figures.



## INTERNATIONAL SEARCH REPORT

National Application No

PCT/FI 99/00329

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/50 A61K9/20 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 383 449 A (ORION-YHTYMÄ OY,FI) 22 August 1990 (1990-08-22) claims 1,2,14,20-23 page 6, line 29 - line 43 ---	1-10
A	WO 92 12135 A (ORION-YHTYMÄ OY,FI) 23 July 1992 (1992-07-23) cited in the application the whole document ---	1-10
A	WO 93 21921 A (ORION-YHTYMÄ OY,FI) 11 November 1993 (1993-11-11) cited in the application the whole document ---	1-10
A,P	WO 99 16443 A (ORION CORPORATION,FI) 8 April 1999 (1999-04-08) the whole document -----	1-10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

2 November 1999

Date of mailing of the international search report

08/11/1999

Name and mailing address of the ISA

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Scarponi, U

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/FI 99/00329

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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			CA 2009678 A,C	11-08-1990
			CN 1044811 A,B	22-08-1990
			DD 293112 A	22-08-1991
			DE 69022078 D	12-10-1995
			DE 69022078 T	22-02-1996
			DK 383449 T	02-01-1996
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			FI 96511 B	29-03-1996
			GB 2228004 A,B	15-08-1990
			GR 3017510 T	31-12-1995
			JP 2288868 A	28-11-1990
			LT 1233 A,B	25-04-1995
			NO 178067 B	09-10-1995
			NZ 232257 A	26-03-1991
			PT 93111 A,B	31-08-1990
			RU 2048467 C	20-11-1995
			SU 1836362 A	23-08-1993
			RU 2068844 C	10-11-1996
			US 5019575 A	28-05-1991
			US 5185332 A	09-02-1993
			US 5122524 A	16-06-1992
WO 9212135	A	23-07-1992	AT 119525 T	15-03-1995
			AU 645399 B	13-01-1994
			AU 1153592 A	17-08-1992
			BG 62002 B	30-12-1998
			BG 97915 A	25-04-1994
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			DE 69201640 D	13-04-1995
			DK 565546 T	22-05-1995
			EP 0565546 A	20-10-1993
			ES 2070627 T	01-06-1995
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			HU 64754 A	28-02-1994
			IE 72101 B	12-03-1997
			IL 100553 A	31-12-1995
			IL 114028 A	12-09-1996
			JP 9183767 A	15-07-1997
			JP 2635445 B	30-07-1997
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			LV 11174 A	20-04-1996
			LV 11174 B	20-12-1996
			NO 300682 B	07-07-1997
			NZ 241194 A	25-06-1993
			PL 169435 B	31-07-1996
			PL 169415 B	31-07-1996
			RO 111847 A	28-02-1997
			SI 9112003 A	31-10-1998
			US 5424428 A	13-06-1995
			US 5569657 A	29-10-1996
			US 5512571 A	30-04-1996

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/FI 99/00329

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9321921	A	11-11-1993	GB 2266841 A	17-11-1993
			AU 4262793 A	29-11-1993
			BG 61678 B	31-03-1998
			BG 99164 A	28-08-1995
			BR 9306314 A	30-06-1998
			CA 2134972 A	11-11-1993
			CZ 9402720 A	15-02-1995
			EP 0639074 A	22-02-1995
			FI 945052 A	27-10-1994
			HU 68956 A	28-08-1995
			JP 7506354 T	13-07-1995
			NO 944145 A	31-10-1994
			NZ 252693 A	27-07-1997
			SK 132494 A	08-11-1995
			US 5512572 A	30-04-1996
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WO 9916443	A	08-04-1999	FI 973804 A	27-03-1999
			AU 9350698 A	23-04-1999
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